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ORIGINAL ARTICLE

Normalization of glomerular filtration rate in obese children

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Abstract
Background Glomerular filtration rate (GFR) is conventionally indexed to body surface area (BSA), but this may lead to biased results when applied to subjects of abnormal body size. The aim of our study was to examine the impact of normalization to the BSA and alternative body size descriptors on measured and estimated GFR in overweight and obese children.
Methods This was a cross-sectional study of 313 children aged 8–9 years old. GFR was measured by 24-h creatinine clearance (CrCl) and additionally estimated from serum creatinine and cystatin C (CysC) using the combined Zappitelli formula, both as absolute values and adjusted to various body size descriptors. The results were compared between 163 normal-weight, 89 overweight and 61 obese children.
Results Compared to the normal-weight children, mean absolute GFR (both measured and estimated) was higher in the overweight and obese children, whereas BSA-adjusted GFR was lower. Linear regression models fitted in normal-weight children revealed equally close associations between absolute GFR and squared height, ideal body weight (IBW) and BSA derived from IBW. Normalization of GFR to the IBW-derived BSA completely eliminated the discrepancy between absolute and BSA-indexed GFR in overweight and obese children.
Conclusions Indexing of GFR to BSA calculated from the ideal—rather than actual—body weight is a promising approach to avoid overcorrection when studying obese children. Further studies should assess the accuracy of this approach across the full range of age and BMI distribution.

Liane Correia-Costa and Franz Schaefer contributed equally as first authors to this work.

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Keywords Glomerular filtration rate · Creatinine clearance · Obesity · Body surface area · Body size · Ideal body weight · Children

Introduction

The current epidemic of obesity is linked to the increase in chronic kidney disease observed in adults over the past few decades, and preliminary evidence suggests that the same effect may emerge in the pediatric population [1]. However, there may be conceptual issues with normalizing glomerular filtration rate (GFR) to body surface area (BSA) in obese individuals. The rationale for indexing GFR to BSA is that normal GFR is proportional to kidney size and the latter is proportional to body size [2]. The BSA correction to 1.73 m^2 was first proposed in 1928 [3] and became widely used in clinical practice as it makes GFR values comparable between adults and children [4]. However, the value of 1.73 m^2 has become outdated due to the recent epidemic of obesity [5]. Moreover, and more importantly, the scaling of GFR to BSA in populations with a wide range of nutritional status is highly controversial [6–8]. Since body mass index (BMI) is strongly correlated with BSA, adjusting for BSA removes any effect of body weight on GFR in epidemiological studies including overweight and/or obese individuals [9]. While GFR adjustment to BSA has limited effects on calculated GFR in subjects with normal body size, an important underestimation of true GFR appears to occur in subjects with higher BMI [9, 10].

Since the number of nephrons is set at birth and does not change with weight gain, an increase in GFR to meet metabolic needs in the obese requires an increase in single-nephron GFR which, according to the concept of kidney symmorphosis, may represent a pathologic rather than physiologic adaptive mechanism [2]. The underestimation of GFR by BSA indexing might conceal these changes [11, 12]. Some authors report that the use of absolute values improves the performance of GFR estimations in adults [13], while others propose that alternative size descriptors should be used for indexing [14–20]. It is probable that the same problems exist in the children regarding the interpretation of BSA-adjusted GFR levels [21]; in addition, the use of absolute GFR is not an option when the target population of the analysis is characterized by a wide age range. Few studies have addressed this issue when comparing normal-weight with overweight/obese children. Here, we utilize a large sample of healthy normal-weight, overweight and obese children to systematically study the impact of indexing to various body size descriptors on measured and estimated GFR.

Methods

Study design and sample

We conducted a cross-sectional study of children aged 8–9 years followed since birth in a cohort study (Generation XXI, Porto, Portugal) [22]. Subjects from the original cohort were eligible for the present study protocol (ObiKid project) if anthropometric data were available and a blood sample had been withdrawn at the 7-year evaluation ($n=4590$), with the exception that they fulfilled any one of the defined exclusion criteria: (1) known presence of a genetic, renal or metabolic disease (including diabetes mellitus); (2) use of medication affecting arterial pressure or glucose or lipid metabolism; (3) use of corticosteroid therapy, both inhaled or systemic, continuously or intermittently in the last 30 days; (4) albumin-to-creatinine urinary ratio of >20 mg/mmol; (5) leukocyturia, nitrituria and hematuria in urinalysis; (6) compliance to a specific diet, such as vegetarianism or use of protein supplements. Our aim was to include a minimum sample of 300 children for the Obikid project's main objective. Assuming a 35 % dropout rate due to refusal to participate, exclusion criteria or incomplete information, 463 children were pre-selected to be consecutively screened according to the date of their 7-year evaluation. Of these 463 children, 16 could not be contacted, 32 refused to participate, 23 were unable to schedule the study visits during the recruitment period and 68 met exclusion criteria [4 chronic diseases (genetic, renal or metabolic); 1 chronic usage of medication (affecting blood pressure, glucose or lipid metabolism), 51 living far from the study site; 12 twins]. Of the 324 enrolled participants, 11 were excluded due to the lack of adequate blood or 24-h urine samples, leaving 313 children for final analysis.

Data collection and variable definition

Anthropometric and general physical examinations were performed according to standard procedures as previously reported [23]. BMI-for-age values were classified into the following categories using the World Health Organization reference data: normal weight [≤+1 standard deviation (SD)], overweight (>1SD and ≤+2SD) and obesity (>2SD) [24]. Classes of gender-specific adequate birth weight for gestational age were defined according to the 2013 revised Fenton growth reference curves [25].

Several body size descriptors were considered as possible GFR adjusters. These were: (1) weight (in kg); (2) squared height (in cm^2); (3) BMI (in kg/m^2) according to the standard formula [weight (in kg) divided by squared height (in m)]; (4) lean body mass (LBM, in kg) calculated by Peters equation [26]; (5) fat-free mass (FFM) (in kg) evaluated by bioimpedance analysis and calculated by Schaefer equation [27]; (6) real BSA (in m^2) calculated by the Haycock formula

[28]; (7) ideal body weight (IBW in kg) inferred by a simple calculation of weight, based on the 50th percentile of BMI-for-age [IBW = BMI at 50th percentile (in kg/m^2) multiplied by squared height (in m)] [24, 29]; (8) BSA using IBW (instead of child's actual weight).

Laboratory procedures

Venous blood samples were collected after an overnight fast and analyzed for creatinine and cystatin C (CysC). A 24-h urine sample was collected from all participants for creatinine analysis. The serum creatinine assay was based on the compensated Jaffé method traceable to an isotope dilution mass spectrometry method (Olympus AU 5400 analyzer; Beckman-Coulter, Brea, CA) [30]. Urinary creatinine was determined using the same clinical chemistry analyzer. Serum CysC was assayed using a particle-enhanced immunonephelometric assay (N latex CysC; Siemens, Erlangen, Germany) before the implementation of the certified reference material (ERM-DA471/IFCC) [31].

Both the Zappitelli combined formula [32] and the Schwartz combined formula [33] were used to estimate GFR (in mL/min/1.73 m^2). Absolute GFR values were calculated by multiplying the eGFR values by BSA and dividing by 1.73 m^2. The 24-h urine samples were considered valid if urinary creatinine was within the range of 11.3–28.0 mg/kg/day and if urinary volume was >300 mL [34]. All children's parents received oral and written information on the correct methods of collection and were asked to register the exact start and end time of the collection; upon 24-h urine sample delivery at the study site the parents were asked to complete a short questionnaire to recheck compliance with the protocol. We excluded 13 urine samples on the basis of inadequate urinary creatinine excretion and two samples in which the collection was deemed incomplete (urinary volume <300 mL and parents referring to errors in the collection). The 24-h creatinine clearance (CrCl; in mL/min;) was calculated in the remaining 298 cases according to the standard formula; this was considered to be the absolute CrCl. To obtain the value generally used in clinical practice, i.e. normalized to 1.73 m^2 of body surface (standard CrCl; in mL/min/1.73 m^2), the absolute CrCl was multiplied by 1.73 and divided by the child's BSA, as defined by the Haycock formula [28]. To test alternative GFR adjusters by the ratio method, absolute GFR/CrCl values were divided by the value of each body size descriptor, thereby obtaining different GFR values adjusted to several body size descriptors.

Statistical analysis

Statistical analysis was performed using the software program SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY). Differences between BMI groups in continuous variables were evaluated with one-way analysis of variance, and those in categorical variables were evaluated with the Chi-square test. Absolute CrCl was regressed on each body size descriptor in separate linear regression models (additionally adjusted for sex and age in months) in the normal weight group in order to test whether the variations in the indexed GFR were only due to differences in body size [19]. The fit of each model was evaluated by the respective R^2 values (coefficients of determination). CrCl adjusted to BSA using IBW (instead of the child's real weight) was regressed separately on weight, height and BMI z score to test the dependence of this renal function estimation on body size. The comparison of CrCl values adjusted to real BSA and BSA using IBW, in normal weight, overweight and obese children, was performed by a paired t test. Measures of association are presented as beta coefficients with 95 % confidence intervals (95 % CI). All p values are two-sided, and $p < 0.05$ was considered statistically significant.

Results

A total of 313 children (53 % male) with a mean (SD) age of 8.8 (0.2) years were included in our analysis. The values of body size descriptors and renal function markers (serum creatinine and CysC) in normal-weight ($n = 163$), overweight ($n = 89$) and obese ($n = 61$) children are presented in Table 1. The mean value of each body size descriptor considered was higher in the overweight and obese groups, as were the serum creatinine and CysC values. Compared to normal-weight children, overweight and obese children were heavier at birth, but no differences were found in the distribution of birth weight adequacy for gestational age. Overweight and obese children presented higher nighttime mean arterial pressure [74.7 ± 5.1 and 75.4 ± 6.4 mmHg, respectively, vs. 73.3 ± 4.8 mmHg (normal-weight children); $p < 0.017$] but similar daytime mean arterial pressure [85.7 ± 5.7 and 86.0 ± 6.5 mmHg, respectively, vs. 84.7 ± 4.6 mmHg (normal-weight children); $p < 0.183$]. No significant differences were found between the groups in the percentage of children presenting a non-dipping pattern (22, 33 and 29 % in normal-weight, overweight and obese groups, respectively; $p = 0.143$).

Compared to normal-weigth children, standard BSA-adjusted eGFR values were lower in overweight and obese children, and measured GFR was lower in obese children (Table 2). By contrast, absolute measured and eGFR values were significantly higher in overweight and obese children. The GFR values adjusted to body size descriptors directly dependent on body weight (weight, BMI and LBM) were significantly lower in overweight and obese children. Conversely, the GFR values adjusted to squared height, FFM, IBW or IBW-derived BSA were significantly higher in overweight and obese children, in concordance with the respective absolute GFR values (Table 2).

Table 1 General characteristics and body size descriptors in normal-weight, overweight and obese children

Patient characteristics	Body weight categories[a]			*p*
	Normal weight	Overweight	Obese	
Age (years)	8.8 (0.3)	8.8 (0.3)	8.8 (0.2)	0.452
Male sex	83 (51 %)	43 (48 %)	40 (66 %)	0.085
Body size descriptors				
Weight (kg)	27.7 (3.3)	35.2 (3.6)	44.3 (6.7)	<0.001
Height (cm)	131.1 (5.4)	134.4 (5.8)	137.5 (5.6)	<0.001
BMI (kg/m^2)	16.0 (1.2)	19.5 (0.9)	23.3 (2.3)	<0.001
BMI *z* score	−0.03 (0.74)	1.56 (0.30)	2.65 (0.48)	<0.001
LBM, by Peters equation (kg)	23.9 (2.5)	28.4 (2.7)	33.4 (4.1)	<0.001
FFM, by Schaefer equation (kg)	20.5 (2.0)	22.4 (2.5)	24.2 (2.1)	<0.001
BSA, by Haycock equation (m^2)	1.00 (0.08)	1.15 (0.08)	1.31 (0.12)	<0.001
IBW (kg)	27.5 (2.3)	28.9 (2.6)	30.3 (2.5)	<0.001
BSA-IBW (m^2)	0.99 (0.06)	1.03 (0.07)	1.07 (0.07)	<0.001
Renal function markers				
Creatinine (mg/dL)	0.43 (0.06)	0.45 (0.06)	0.45 (0.06)	0.003
Cystatin C (mg/L)	0.64 (0.07)	0.67 (0.08)	0.68 (0.06)	<0.001

Values in table are presented as the mean, with the standard deviation (SD) in parenthesis or as a number with the percentage in parenthesis, as appropriate

BMI, Body mass index; LBM, lean body mass (estimated by Peters' equation) [26]; FFM, fat-free mass (estimated by Schaefer's equation) [27]; BSA, body surface area (calculated by the Haycock equation [28]); IBW, ideal body weight; BSA-IBW, body surface area calculated by Haycock equation, using IBW instead of child's real weight

[a] The normal weight, overweight and obese groups were defined according to the World Health Organization classification for BMI *z* score [24]

To identify the body size descriptor that best reflects variation in kidney function with body size, we fitted separate linear regression models, with absolute CrCl (mL/min) as the dependent variable and each body size descriptor as the independent variable, considering only normal-weight children. The models incorporating squared height, IBW or IBW-derived BSA had the highest coefficients of determination (R^2), each explaining about 15 % of the absolute CrCl variation (Table 3). Among these three variables, IBW-BSA adjustment is probably the most practical because (1) BSA adjustment is already widely used in clinical practice and (2) adjustment to BSA using IBW would only require a minor adaptation. The CrCl adjusted to IBW-BSA was independent of weight (β 1.14, 95 % CI −0.54 to 2.82; $p=0.184$), height (β 0.70, 95 % CI −0.34 to 1.73; $p=0.186$) and BMI *z* score (β 3.41, 95 % CI −3.98 to 10.80; $p=0.363$). Bland–Altman plots conveying the comparison between the Schwartz and Zappitelli standard formulas (BSA adjusted) and between each of these formulas adjusted to BSA-IBW and the standard BSA-adjusted CrCl are presented in Electronic Supplementary Material Figs. 1, 2 and 3 for normal-weight, overweight and obese children, respectively.

In our entire sample, no significant differences were found between BSA-adjusted and IBW-BSA-adjusted CrCl values in normal-weight children [162 (SD 34) vs. 162 (SD 34) mL/min/1.73 m^2, respectively; $p=0.897$]. However, BSA-adjusted CrCl values were significantly lower than IBW-BSA-adjusted CrCl values in both the overweight [152 (32) vs. 169 (34) mL/min/1.73 m^2, respectively; $p<0.001$] and obese [161 (26) vs.196 (31) mL/min/1.73 m^2, respectively; $p<0.001$) groups, in accordance with absolute CrCl values (Table 2).

Discussion

The aim of our study was to evaluate the impact of GFR normalization using different anthropometric descriptors of body size in children of normal or increased body weight. We subsequently identified important inconsistencies introduced by GFR adjustment for body size in overweight and obese children, with normalization to conventional BSA or other body size descriptors dependent on weight yielding systematically lower GFR estimates in these children than in normal-weight children. Conversely, when GFR was expressed by absolute values or those adjusted for height, IBW or IBW-derived BSA, we obtained higher values of measured and estimated GFR for the overweight and obese groups. Hence, the method of adjustment for body size is a major confounder of GFR determination in children with abnormal body habitus.

Although recognizing the lack of a solid reference standard for GFR, we decided to use it as our reference standard, taking

Table 2 Absolute and adjusted estimates of glomerular filtration rate in normal-weight, overweight and obese children

Estimates of GFR[a]	Body weight categories			*p*
	Normal weight	Overweight	Obese	
Absolute CrCl (mL/min)	93.2 (21.0)	101.4 (21.4)	120.8 (21.5)	<0.001
Absolute GFR, by Zappitelli formula (mL/min)	79.8 (10.5)	87.8 (11.6)	100.1 (14.4)	<0.001
Absolute GFR, by Schwartz formula (mL/min)	65.1 (8.3)	73.1 (9.1)	83.2 (12.5)	<0.001
Weight-adjusted CrCl (mL/min/kg)	3.4 (0.7)	2.9 (0.6)	2.8 (0.5)	<0.001
Weight-adjusted GFR, by Zappitelli formula (mL/min/kg)	2.9 (0.4)	2.5 (0.3)	2.3 (0.2)	<0.001
Weight-adjusted GFR, by Schwartz formula (mL/min/kg)	2.4 (0.3)	2.1 (0.2)	1.9 (0.2)	<0.001
Squared height-adjusted CrCl (mL/min/cm^2)	54.3 (11.4)	55.9 (11.4)	64.0 (10.0)	<0.001
Squared height-adjusted GFR, by Zappitelli formula (mL/min/cm^2)	46.4 (5.4)	48.6 (5.9)	52.8 (5.9)	<0.001
Squared height-adjusted GFR, by Schwartz formula (mL/min/cm^2)	37.8 (3.9)	40.5 (4.1)	43.8 (5.0)	<0.001
BMI-adjusted CrCl (mL/min/kg/m^2)	5.8 (1.4)	5.2 (1.2)	5.2 (1.0)	<0.001
BMI-adjusted GFR, by Zappitelli formula (mL/min/kg/m^2)	5.0 (0.7)	4.5 (0.6)	4.3 (0.5)	<0.001
BMI-adjusted GFR, by Schwartz formula (mL/min/kg/m^2)	4.1 (0.5)	3.8 (0.5)	3.6 (0.4)	<0.001
LBM-adjusted CrCl (mL/min/kg)	3.9 (0.8)	3.6 (0.7)	3.7 (0.6)	0.001
LBM-adjusted GFR, by Zappitelli formula (mL/min/kg)	3.4 (0.4)	3.1 (0.4)	3.0 (0.3)	<0.001
LBM-adjusted GFR, by Schwartz formula (mL/min/kg)	2.7 (0.3)	2.6 (0.3)	2.5 (0.2)	<0.001
FFM-adjusted CrCl (mL/min/kg)	4.6 (1.0)	4.6 (1.1)	5.0 (0.9)	0.012
FFM-adjusted GFR, by Zappitelli formula (mL/min/kg)	3.9 (0. 6)	4.0 (0.7)	4.1 (0.6)	0.037
FFM-adjusted GFR, by Schwartz formula (mL/min/kg)	3.2 (0.5)	3.3 (0.5)	3.4 (0.5)	0.002
IBW-adjusted CrCl (mL/min/kg)	3.4 (0.7)	3.5 (0.7)	4.0 (0.6)	<0.001
IBW-adjusted GFR, by Zappitelli formula (mL/min/kg)	2.9 (0.3)	3.0 (0.4)	3.3 (0.4)	<0.001
IBW-adjusted GFR, by Schwartz formula (mL/min/kg)	2.4 (0.2)	2.5 (0.3)	2.7 (0.3)	<0.001
BSA-IBW-adjusted CrCl (mL/min/1.73 m^2)	161.9 (34.3)	169.2 (34.1)	195.6 (30.9)	<0.001
BSA-IBW-adjusted GFR, by Zappitelli formula (mL/min/1.73 m^2)	138.6 (16.0)	146.9 (17.3)	161.6 (18.5)	<0.001
BSA-IBW adjusted GFR, by Schwartz formula (mL/min/1.73 m^2)	112.9 (11.7)	122.3 (12.3)	134.2 (15.9)	<0.001
Standard CrCl (BSA adjusted) (mL/min/1.73 m^2)	162.0 (34.4)	152.4 (31.5)	160.7 (26.3)	0.077
Standard GFR (BSA adjusted), by Zappitelli formula (mL/min/1.73 m^2)	138.5 (15.7)	132.3 (16.2)	132.1 (13.0)	0.002
Standard GFR (BSA adjusted), by Schwartz formula (mL/min/1.73 m^2)	112.7 (11.2)	110.1 (11.1)	109.6 (10.4)	0.069

Values in table are presented as the mean with the SD in parenthesis

GFR, Glomerular filtration rate; CrCl, 24-h creatinine clearance. See Table 1 footnote for all other abbreviations

[a] Absolute GFR values were derived from the Zappitelli or Schwartz combined formulas by multiplying the standard GFR values by the children's BSA and dividing by 1.73 m^2 . Adjusted GFR values for each size descriptor were obtained by dividing the absolute GFR by the value of the size descriptor of each child

care to include only correctly timed 24-h collections. The finding of an increased absolute GFR in both the overweight and obese children is consistent with the notion of glomerular hyperfiltration as the initial stage of obesity-associated renal dysfunction [35, 36]. It should be noted that the higher levels of creatinine and CysC found in our overweight/obese children may result from these children being slightly taller and possibly thereby presenting higher levels of muscle mass or body fat mass [37, 38], both of which are known to interfere with each one of the markers used. Analysis of unadjusted GFR in pediatric studies is only possible if the population of interest is limited to a narrow range of body size, as in this assessment of 8- to 9-year-old children. Studies encompassing a wider age range mandate either the use of percentiles, as proposed by Piepsz et al. [39], or adjustment of GFR for some measure of body size. Since pediatric percentiles of absolute GFR are currently not available for any methodology of GFR measurement other than the largely abandoned radioactive ^{51}Cr-EDTA clearance method, we considered it to be more useful to identify an alternative body size descriptor to replace BSA to normalize both measured and estimated GFR. For that purpose we compared the association between several body size descriptors and absolute CrCl in order to identify the variables most closely related to variations in GFR. This part of the analysis was restricted to normal-weight children to rule out any potential obesity-related bias. Squared height, IBW and IBW-based BSA were found to be equally closely correlated to absolute GFR. In fact, these are all anthropometric

Table 3 Influence of several body size descriptors on absolute 24-h creatinine clearance in normal weight children

Absolute CrCl (mL/min)	Intercept (95 % CI)	β (95 % CI)	R^2
Weight (kg)	110.56 (−3.27 to 224.39)	1.909 (0.920 to 2.899)**	0.111
Squared height (cm^2)	64.22 (−48.52 to 176.95)	0.005 (0.003 to 0.008)**	0.149
BMI (kg/m^2)	94.81 (−25.66 to 215.29)	1.539 (−1.219 to 4.297)	0.033
LBM, by Peters equation (kg)	104.61 (−7.66 to 216.88)	3.280 (1.796 to 4.763)**	0.135
FFM, by Schaefer equation (kg)	53.68 (−71.29 to 178.65)	2.406 (0.622 to 4.189)*	0.071
BSA, by Haycock equation (m^2)	78.40 (−35.13 to 191.93)	88.653 (46.862 to 130.444)**	0.127
IBW (kg)	82.83 (−29.11 to 194.78)	3.342 (1.915 to 4.769)**	0.147
BSA-IBW (m^2)	44.44 (−70.01 to 158.89)	125.871 (72.486 to 179.257)**	0.148

*$p < 0.050$; **p value < 0.001

Each row represents a separate multiple linear regression of the absolute 24-h CrCl on the corresponding independent variable. All analyses were adjusted for sex and age. The regression coefficients are given per unit

95 % CI, 95 % Confidence interval. See footnotes to Tables 1 and 2 all other abbreviations

indicators that reflect body size independently of adiposity. We propose that IBW-BSA be used to normalize GFR in obese children, as this approach will still allow comparisons with the standard GFR values used in clinical practice.

The impact of using IBW rather than actual weight to calculate BSA in obese children is evident both from the application of the normalization method to the whole study sample and from the use of a practical example. Let us consider two 9-year-old boys of the same height but different body weight whom we assume have the same renal function (absolute CrCl 80 mL/min). The normal-weight boy has similar values of BSA derived from his actual and IBW and, therefore, presents a minimal difference in the respective adjusted CrCl values. In the obese boy, actual BSA is 1.30 m^2 whereas the IBW-derived BSA equals that of the normal-weight boy, resulting in a difference in adjusted CrCl of about 20 mL/min/1.73 m^2 (CrCl adjusted to BSA: 106.5 mL/min/1.73 m^2 vs. CrCl adjusted to BSA-IBW: 127.0 mL/min/1.73 m^2). Thus, equivalent to the findings with uncorrected GFR, IBW-BSA adjusted GFR is increased in overweight and obese children.

The use of IBW-derived BSA for GFR normalization has been postulated previously [8] and recently also found to avoid overcorrection in obese adults [40]. Another study in adults, aimed at determining the influence of GFR on drug clearance, also found that the use of IBW in a GFR formula including body weight increased the probability of achieving effective therapeutic exposure [41]. In children, the usefulness of calculating BSA from IBW has been recognized in other clinical settings, such as indexing ventricular mass, after acknowledging that the standard method using actual BSA led to underestimation of the volume load in obese patients [42]. Another study in adults identified total body water as the best adjuster and proposed that a standardized value of total body water should replace the current practice of normalizing GFR to 1.73 m^2 BSA [18]. However, in clinical practice total body water is estimated by anthropometric equations incorporating weight and would therefore be likely to cause the same overcorrection as BSA when applied in obese individuals [39].

The large sample size of healthy children across all BMI classes can be considered to be a major strength of this study, as is the high methodological standardization of 24-h collection and the use of an equation for GFR estimation combining CysC and creatinine. The use of an endogenous clearance technique to measure GFR represents a limitation since this method is known to overestimate GFR by at least 10 % because of active creatinine excretion by the renal tubules [43, 44]. Evaluation of the accuracy of equations on GFR estimation when compared to CrCl in this group of children was performed in a previous study of our group [45]. Other important limitations of our study are the restriction of the analysis to a single pediatric age group and the fact that BSA was estimated and not directly measured. We intend to confirm our findings in future studies using exogenous GFR measurements in children with a wider range of age and also with chronic kidney disease, thereby extending the ability to generalize our conclusions.

In light of our results and those from the relevant literature, we believe that alternative ways to index GFR need to be considered in the setting of pediatric obesity. While assessment of absolute GFR without any indexation may represent an appropriate approach in cohorts with substantial variation of fat mass and is suitable for intra-individual longitudinal analyses, it does not allow comparisons with reference values and with children across the pediatric age range. Normalization of GFR to BSA calculated from IBW rather than actual weight is a promising option that deserves further investigation across all pediatric age groups, ideally in healthy children.

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Compliance with ethical standards

Conflict of interest None of the authors have any financial or nonfinancial competing interests concerning the present study.

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Ethics The ObiKid project was approved by the Ethics Committee of Centro Hospitalar São João, Porto, Portugal, and by the Faculty of Medicine of the University of Porto and complies with the Helsinki Declaration and the current national legislation. Written informed consent from parents (or their legal substitute) and verbal assent from children was obtained.

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